IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner:
Steven M. Reppert	)	
	:	Group Art Unit:
Application No.:	)	
	:	
Filed: Unknown	)	
	:	
For: High Affinity Melatonin Receptors And Uses Thereof	)	May 19, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231
ATTENTION: Office of Petitions
Crystal Park 1
Room 520

PROTEST UNDER 37 C.F.R. §1.291(a)

Sir:

According to 37 C.F.R. §1.291(a), the undersigned hereby files a protest against the United States patent application corresponding to European patent application number 95922284.5, which, in turn, corresponds to International patent application number PCT/US95/07360 (publication number WO 95/35320), filed on June 7, 1995. The inventor named in the International application is Steven M. Reppert; the applicant named is The Massachusetts General Hospital. The International application claims an earliest priority date of June 17, 1994 to United

States patent application number 08/261,857 and was published on December 28, 1995. As published, the International application contained claims 1-36, and upon entry into the regional European phase, the application contained claims 1-20. Claim 36 of the International application and claim 20 of the European application are identical; its corresponding claim in the U.S. application is the subject matter of the instant protest. Claim 36 of the International application is directed to:

> A therapeutic composition comprising as an active ingredient high-affinity melatonin receptor agonist, said active ingredient being formulated in a physiologically-acceptable carrier.

The Protestor alleges that the claim in the U.S. patent application corresponding to claim 36 of the International application fails to comply with the patent laws of the United States, specifically 35 U.S.C. §§ 102, 103 and 112. Set forth below are arguments supporting the allegations, as well as references the Protestor contends either anticipate or render obvious the claim at issue.

The International application relates generally to DNA sequences encoding high-affinity melatonin receptor proteins localized to the brain and retina, designated melatonin receptors 1a and 1b, respectively. The claims also relate to substantially

pure polypeptide fragments of both high-affinity melatonin receptors 1a and 1b. Additionally, the document explains a method of screening candidate compounds for the ability to act as either agonists or antagonists of the high-affinity melatonin receptors.

The Protestor contends that a claim equivalent in scope to claim 36 of the International application written in a U.S. patent application fails to comply with 35 U.S.C. § 112, ¶ 2 for failure to particularly point out and distinctly claim the subject matter the applicant regards as the invention. The only limit placed on melatonin receptor agonist as claimed is that it be a high-affinity agonist, which would not allow one of ordinary skill in the art to determine the precise scope, e.g., the metes and bounds of the claim.

Although the International application discloses a testing method for screening compounds that may act as agonists or antagonists for the interaction between melatonin and its high-affinity receptors, the specification fails to teach one skilled in the art how to identify which compounds, of all those known in the universe, may serve as putative agonists, other than the suggestion that "[a]ppropriate candidate agonists include melatonin analogs or other agents which mimic the action of

melatonin." (International application, page 52, lines 32-34).

The International application discloses that melatonin agonists may be useful in treating circadian rhythm disorder in humans as well as regulating changes in reproductive cycles in seasonally breeding animals. For instance, page 57, line 28 to page 58, line 1 teaches that:

> High-affinity melatonin receptor agonists can be used to reentrain the endogenous melatonin rhythm of humans; alleviate jet lag symptoms in humans; phase shift the sleep/wake cycle of some blind people, reinforce entrainment of endogenous melatonin rhythm using low intensity light/dark cycle; control ovulation in humans; and alter reproductive cycles in seasonally breeding animals.

The effects described in the International application were all well-known prior to the date Applicant filed for patent protection as indicated by the references filed herewith. Because there is no disclosure of acceptable melatonin agonists, other than melatonin itself, the Protestor contends that a claim of equivalent scope in a U.S. patent application would fail to comply with 35 U.S.C. § 112, ¶ 1 as failing to enable any person skilled in the art to make and use the invention.

The Protestor respectfully directs the Examiner's attention to the enclosed documents that either anticipate or render obvious a claim equivalent to claim 36 of the International application.

For the Examiner's convenience, the references discussed below are also listed on the enclosed PTO Form 1449.

Document 1 S.P. Fraser et al., "Melatonin receptor mRNA expression in *Xenopus* oocytes: inhibition of G-protein-activated response" *Neuroscience Letters*, 124 (1991), 242-45.

Document 2 M.L. Dubocovich, "Pharmacology and function of melatonin receptors" *The FASEB Journal*, 2(1988), 2765-2773.

Document 3 L.L. Carlson et al., "Melatonin signal transduction in hamster brain: inhibition of adenylyl cyclase by a pertussis toxin-sensitive G protein" *Endocrinology*, Vol. 125, No. 5, 1989, 2670-2676.

Documents 1-3 were cited by the Examiner in the International Preliminary Examination Report as anticipating Claim 36 of that application by disclosing melatonin as a high-affinity melatonin receptor agonist that can be used as a therapeutic composition. The Protestor agrees with the Examiner that the cited references demonstrate that pharmaceutical compositions containing melatonin were well known prior to Applicant's invention.

Document 4 U.S. Patent Number 5,194,614

The '614 patent was issued March 16, 1993, which is earlier than the earliest priority date claimed by the International application.

The invention disclosed in the '614 patent relates to new compounds of 1-alkoxy-(2-acylaminoethyl)naphthalenes, processes for preparing and pharmaceutical compositions containing same. The patent teaches that pharmaceutical compositions of the compounds bind to melatonin receptors with an affinity superior to that of melatonin itself (col. 17, lines 44-48), and that the compounds are useful in treating a variety of human disorders, including seasonal depression, insomnia, and jet lag (col. 4, lines 25-54). The compounds disclosed in the patent fall within the category of "agonists" defined in the specification of the International application as "a molecule that mimics...the ability of a high-affinity melatonin receptor ligand to bind a high-affinity melatonin receptor and to trigger the biological events resulting from such an interaction...."

The Protestor contends that, according to 35 U.S.C. § 102, the '614 patent anticipates a claim in a U.S. application equivalent in scope to claim 36 of the International application.

Document 5 U.S. Patent Number 5,240,919

The '919 patent issued August 31, 1993, which is earlier than the earliest priority date claimed by the International application.

The '919 patent relates to new heterocycle-substituted alkylamides and processes for preparing and pharmaceutical compositions of same. The '919 patent discloses that compounds of the invention "possess the property of binding with very high affinity to melatonin receptors." (col. 1, lines 14-16). The '919 patent teaches the results of a pharmacological study concluding that the inventive compounds "are of low toxicity and endowed with appreciable affinity for melatonin receptors, and that, in addition, they substantially increase melatin synthesis by the pineal gland." (Col. 8, lines 19-23).

Pharmaceutical compositions containing the compounds of the '919 patent are discussed at col. 8, lines 47-61. Columns 39-41 outline experiments that demonstrate compounds of the invention act as high-affinity melatonin receptor agonists, consistent with the definition found in the specification of the International application.

Consequently, the Protestor contends that, according to 35 U.S.C. § 102, the '919 patent anticipates a claim in a U.S.

patent application equivalent in scope to claim 36 of the International application.

Document 6 U.S. Patent Number 5,276,051

The '051 patent issued January 4, 1994, which is earlier than the earliest priority date claimed by the International application.

The '051 patent relates to arylethylamine compounds, processes for preparation and pharmaceutical compositions of same. The compounds display an affinity for the melatonin receptor that is superior to that of any compounds previously described in the literature and possess pharmacological activities as both agonists and antagonists of melatonin (col. 1, lines 31-39).

Pharmacological properties of the compounds are disclosed at columns 6-7. Demonstration of binding of the compounds to melatonin receptors is described at Example A in column 16, while pharmaceutical compositions, including lists of excipients are discussed at column 7, lines 21-30.

Consequently, the Protestor contends that, according to 35 U.S.C. § 102, the '051 patent anticipates a claim in a U.S. patent application equivalent in scope to claim 36 of the

International application.

Document 7 EP-A-0,591,057, which corresponds to U.S. Patent Number 5,464,872.

The '057 European patent was published April 6, 1994, which is earlier than the earliest priority date claimed by the International application.

The corresponding U.S. patent (the '872 patent) to the '057 European patent is directed to new arylalkyl(thio)amides, processes for preparing and pharmaceutical compositions of same. The patents teach that the compounds posses "considerable activity with respect to the melatoninergic system" (the '872 patent, col. 1, lines 18-25). Column 7, lines 40-61 of the '872 patent discuss pharmaceutical compositions for the compounds and list human conditions for which the compounds may be used as treatment. Column 22, lines 51-67 of the U.S. patent outline experiments that demonstrate that the compounds of the invention specifically bind to melatonin receptors.

Consequently, the Protestor contends that, according to 35 U.S.C. § 102, EP-A-0,591,057, which corresponds to U.S. Patent Number 5,464,872 anticipates a claim in a U.S. patent application equivalent in scope to claim 36 of the International application.

Document 8 **Yous et al., "Novel naphthalenic ligands with high affinity for the melatonin receptor"** ***Journal of Medicinal Chemistry*****, Vol. 35 (1992), 1484-1486.**

The article was published in 1992, which is earlier than the earliest priority date claimed by the International application.

The article describes chemical synthesis of melatonin receptor analogs and their uses for rapidly screening receptor binding potency. The author concludes that modifications may be made to both the indole nucleus and the acylamino group of the melatonin molecule thereby affecting binding affinity of the melatonin analogs to the melatonin high-affinity receptor.

Because the article also discloses a role for melatonin in the regulation of human sleep, seasonal disorders, depression and ageing, the Protestor contends that a skilled artisan would be motivated to employ the disclosed compounds in a pharmaceutically acceptable composition, thereby rendering obvious under 35 U.S.C. § 103 a claim in a U.S. patent application equivalent in scope to claim 36 of the International application.

Document 9 **G. Spadoni et al., "2-Substituted 5-Methoxy-N-acyltryptamines: synthesis, binding affinity for the melatonin receptor, and evaluation of the biological activity" *Journal of Medicinal Chemistry*, Vol. 36 (1993), 4069-4074.**

The paper was published in 1993, which is earlier than the earliest priority date claimed by the International application.

The paper describes the synthesis of certain melatonin analogs derived from the structure of the melatonin molecule. Biological experiments both *in vivo* and *in vitro* indicate that the newly synthesized analogs act as either melatonin agonists or antagonists, as shown in table IV at page 4071. The *in vivo* tests conducted by the authors clearly suggest that formulating the described compounds in a pharmaceutically acceptable carrier to yield therapeutic compositions would not be beyond the purview of one ordinarily skilled in the art. Consequently, the reference renders obvious under 35 U.S.C. § 103 a claim in a U.S. patent application equivalent in scope to claim 36 in the International application.

Document 10 **S.M. Reppert et al., "Putative melatonin receptors in a human biological clock" *Science*, Vol. 242 (1988), 78-81.**

The article was published in 1988, which is before the earliest priority date claimed in the International application.

The authors describe use of three compounds, including 6-chloromelatonin, as high-affinity melatonin receptor agonists, characterized by their ability to interfere with radioactively labeled melatonin and its receptor.

Additional experiments localize the site of high-affinity melatonin receptors to specific areas in the brain. In conclusion, the paper contemplates use of melatonin in a pharmaceutical composition as an effective treatment for jet lag and sleep disorders. Consequently, the article acts as an anticipatory reference under 35 U.S.C. § 102 or, alternatively, renders obvious under 35 U.S.C. § 103 a claim in a U.S. patent application equivalent in scope to claim 36 of the International application.

Document 11 S.W. Ying et al., "Human malignant melanoma cells express high-affinity receptors for melatonin: antiproliferative effects of melatonin and 6-chloromelatonin" *European Journal of Pharmacology - Molecular Pharmacology Section*, Vol. 246 (1993), 89-96.

The article was published in 1993, which is before the earliest priority date claimed by the International application.

The paper suggests that melatonin and two of its agonistic analogs, 6-chloromelatonin and 2-iodomelatonin, suppress proliferation of cancerous human cells *in vitro* through binding

to high affinity melatonin receptors. While the experiments conducted in the paper do not utilize pharmaceutical compositions of melatonin agonists, one of ordinary skill in the art would certainly be motivated to synthesize the described agonists with the appropriate physiologically acceptable carriers for administration to humans. Consequently, the paper renders obvious under 35 U.S.C. § 103 a claim in a U.S. patent application equivalent in scope to claim 36 of the International application.

Document 12 E. Duranti et al., "2-Bromomelatonin: synthesis and characterization of a potent melatonin agonist" *Life Sciences*, Vol. 51 (1992) 479-485.

The paper was published in 1992, which is before the earliest priority date claimed by the International application.

The authors discuss the prevalence of research into melatonin analogs, specifically 2-iodomelatonin, and how potential research into melatonin receptors and human clinical applications involving melatonin may be hampered by the tedious and expensive preparation of melatonin agonists. The authors report the simple synthesis of a new melatonin analog, 2-bromomelatonin, and demonstrate *in vivo* that the analog acts as an effective melatonin agonist within the definition in the

International application. While the *in vivo* studies were conducted in rabbits and hamsters, one of ordinary skill in the art would be motivated to develop the compound with pharmaceutically acceptable vehicles for delivery *in vivo* to humans. Therefore, the paper renders obvious under 35 U.S.C. § 103 a claim in a U.S. patent application equivalent in scope to claim 36 of the International application.

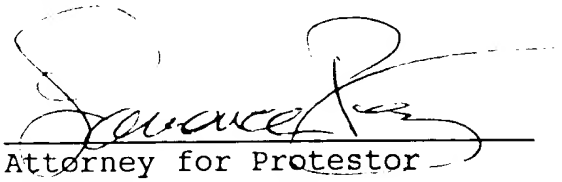
Conclusion

The Protestor respectfully requests that the Examiner consider the arguments and references presented above during examination of a U.S. patent application equivalent in scope to the International application.

Applicant believes that no fee is required. However, the Assistant Commissioner is authorized to charge any fees required to Deposit Account No. 06-1205.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should be directed to our below listed address.

Respectfully submitted,



Attorney for Protestor
Lawrence S. Perry
Registration No. 31,865

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

Certificate of Service

I hereby certify that on this 19th day of May, 1999, a true and correct copy of the foregoing Protest Under 37 C.F.R. § 1.291(a) was mailed by first-class mail postage paid, to:

Paul T. Clark, Esq.
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804

Lawrence S. Perry

NY_MAIN 4254 v 1